The use of ACE inhibitors, Statins and Omega-3 may ameliorate Cardio-toxicity of the Doxorubicin

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Keywords: Cardio toxicity, Pharmacology, Toxicology

Abstract

Doxorubicin, also known as hydroxydaunorubicin, is an anthracycline antibiotic, its structure is closely related to the natural product daunomycin, and like all anthracyclines, works by inhibiting DNA replication. Doxorubicin is very beneficial in treatment of different types of cancer such as liver or breast cancer, its importance is unquestionable in arresting the size of tumor but its cardio toxicity limits its usefulness. There are different mechanisms involved in its cardio toxicity such as the release of free radicals, apoptosis, necrosis and autophagy of cardio myocytes. Doxorubicin-induced heart damage may be due to an increase in cardiac oxidative stress, as indicated by Reactive Oxygen Species (ROS) induced damage such as lipid peroxidation, along with reduced levels of antioxidants and mercapto groups (SH). It was found that irregularities in myofibrillar and intracellular calcium are also important mechanisms for doxorubicin-induced cardiac toxicity. There are at least two targets for doxorubicin-induced apoptosis; it was found that cardiac cells and endothelial cells are affected by doxorubicin-induced apoptosis, as evidenced by caspase activation and internucleosomal DNA damage. Additionally, the changes in the high-energy phosphate pool, endothelin-1 levels, and disturbances of myocardial adrenergic signaling are the most suggested causing factors of cardiac toxicity associated with doxorubicin administration. Therefore, there are different trials aiming to suppress its cardio toxicity to widen its use. Here, in this abstract, we discussed that how much the use of captopril, omega 3 and rosuvastatin could reduce the doxorubicin induced cardio toxicity.

Captopril is an example of angiotensin converting enzyme inhibitor (ACEI), and largely is used in treatment of hypertension, heart failure and diabetic nephropathy. Additionally, captopril has anti-inflammatory and antioxidant properties due to inhibition of angiotensin ii formation and because of its structure which contains sulfhydryl group (SH) with high antioxidant properties. Magda Nasr et al., (2013) found that captopril (25mg/kg for 21 days) inhibited the cardio toxicity of doxorubicin which induced by intra-peritoneal (IP) injection of (12 mg/kg) doxorubicin in male mice. Moreover, it succeeded into reducing the cardiac level of tumor necrosis factor (TNF) which is a valid parameter of inflammatory mediators and increasing the cardiac level of antioxidant parameters such as super oxide dismutase (SOD) and glutathione in reduced form (GSH).

Rosuvastatin is the latest statin which causes a potent inhibition for 3-hydroxyl-3- methylglutaryl coenzymeA (HMG-CoA) reductase enzyme. Recently, rosuvastatin succeed to inhibit SRC/FAK pathway in liver cancer in addition to RAS/RAF and STAT-3 pathways in the study of Ibrahim Elsayed et al., 2018. Interestingly, rosuvastatin increased the antitumoral effect of dasatinib and reduced the inhibitory concentration (IC50) of dasatinib in HEPG2 cell line (in-vitro study) in Ibrahim Elsayed et al.,(2018). Statins have been shown to arrest tumor and normal cells in the G1 phase of the cell cycle, inducing a potent apoptotic effect. Statins are also known to have antioxidant properties by reducing free radical generation in the vascular wall and in the myocardium during ischemia reperfusion. In the study of Magda Nasr et al., (2013) rosuvastatin not only ameliorated the cardio toxicity of doxorubicin but also prompted the antitumoral effect of doxorubicin. Moreover, rosuvastatin (20 mg/kg/day) for 21 days reduced the level of cardiac inflammatory mediators (TNF) and subsequently increased the level of antioxidant parameters (GSH and SOD) in cardiac myocytes. Rosuvastatin is a promising drug to be used in different types of tumor alone or in combination as in case of doxorubicin to reduce the suspected dose of doxorubicin aiming to reduce the doxorubicin induced cardio toxicity. Therefore, we advise to start clinical trials using rosuvastatin in patients suffering from liver cancer.

Omega-3 is poly unsaturated fatty acid (eicosapentanoic acid and decosahexanoic acid) has been shown to reduce the size of solid tumors and enhance the antitumoral effects of chemotherapeutic drugs. Omega- 3 has potent anti-angiogenic effect, inhibiting production of many important angiogenic mediators including VEGF and PDGF. Omega-3 is well known to reduce systemic inflammation and oxidative free radicals – all processes that have been linked with doxorubicin induced cardio toxicity. The elevated cardiac level of TNF surpassed by doxorubicin (12 mg/kg) was declined by omega-3 (1 gm/kg/day for 21 days) treatment. Moreover, omega 3 increased the cardiac levels of antioxidant parameters (GSH and SOD). Additionally, Uygur et al. demonstrated the cardio protective effects of fish omega-3 fatty acids on doxorubicin-induced cardio toxicity in rats. Omega-3 (400 mg/kg/day) was given for 30 days by intragastric intubation. Doxorubicin (30 mg/kg) was injected intraperitoneally by a single dose to induce acute cardio toxicity. The doxorubicin-treated group with fish n-3 fatty acids therapy caused a significant reduction in the activity oterminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick end labeling in cardio myocytes. Furthermore, in contrast to the results of El-Sayed et al., the doxorubicintreated with fish n-3 fatty acids group showed a significant decline in malondialdehyde level, and an increase in superoxide dismutase and glutathione peroxidase activities when comparedto the doxorubicin-treated group It was concluded that the both studies examined the cardio protective effects of omega-3 as anti-oxidant or anti-apoptotic drug.

Therefore, the use of captopril, rosuvastatin and omega3 proved their success in limiting the doxorubicin induced cardio toxicity due to their anti-inflammatory and antioxidant properties. Surprisingly, the use of rosuvastatin markedly increased the antitumoral effect of doxorubicin in the liver cancer. Therefore, clinical trials for using rosuvastatin in different types of tumor or in different combination with well-established anti tumoral drugs should be done in the near future.

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